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Non-monotonic power in Bayesian dynamic borrowing: insights and practical remedies

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Motivation: non-inferiority oncology trial

RCT to compare two different therapies for treating a cancer that originates in the appendix:

- High-dose regimen ("Dutch protocol", most used)
- Low-dose regimen (cheaper and *safer*, used in the UK centre)

Can we conclude that the low dose is **not less effective** than high dose?

Endpoint: **2-year disease-free survival (DFS)**

$$Y_j \sim Bernoulli(p_j), \qquad j = \{High, Low\}$$

with Bayesian priors on survival rates p_j's based on historical data

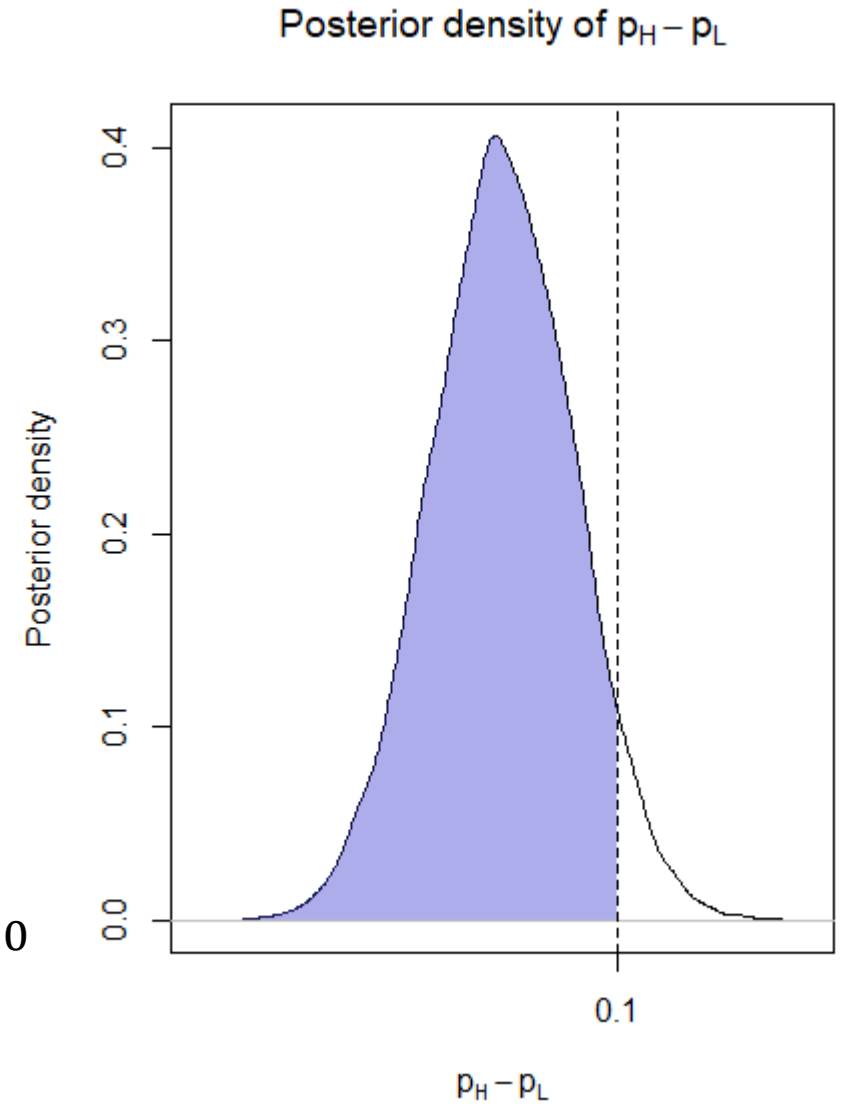
Bayesian decision-making

Hypotheses of non-inferiority trial:

- H_0 : Difference in survival rates ($p_H - p_L$) is **larger or equal to** 0.1 (**low-dose is inferior)**
- H_1 : Difference in survival rates ($p_H - p_L$) is **smaller** than 0.1 (**low-dose is not inferior)**

We claim non-inferiority of low-dose regimen if $P(p_H - p_L < 0.1 | data) > \xi$

N.B. ξ calibrated to control type I error under specific H_0



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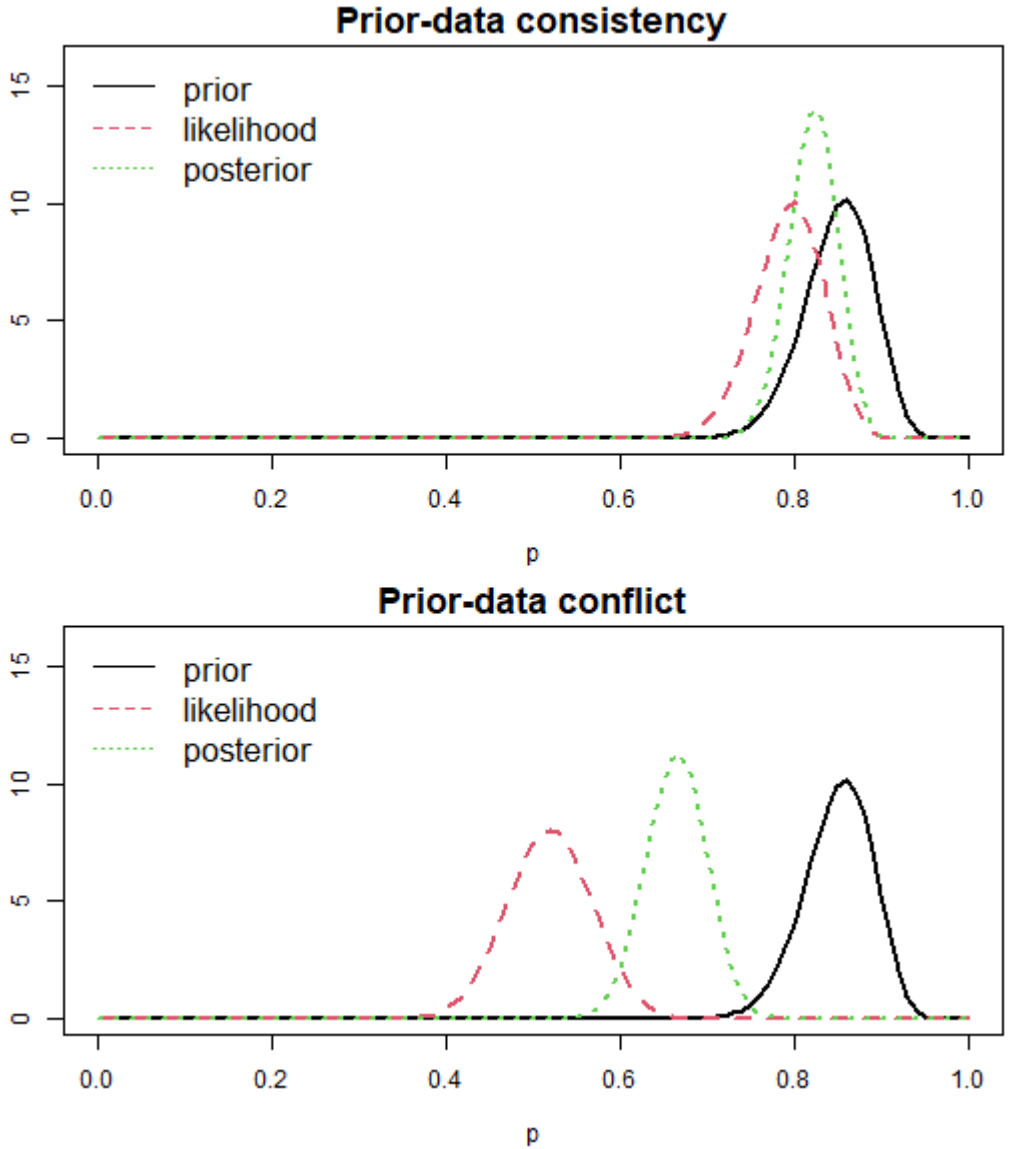
Prior elicitation from historical data

Prior distributions based on historical survival rates and degree of relevance of past studies (conjugate Beta, MAP, etc.)

Benefit: If new and past study data are ***consistent,*** we gain **efficiency**
(=smaller sample size to achieve same power)

Risk: In case of **conflict**, a too informative prior can **increase the chance of making wrong conclusions (!)**



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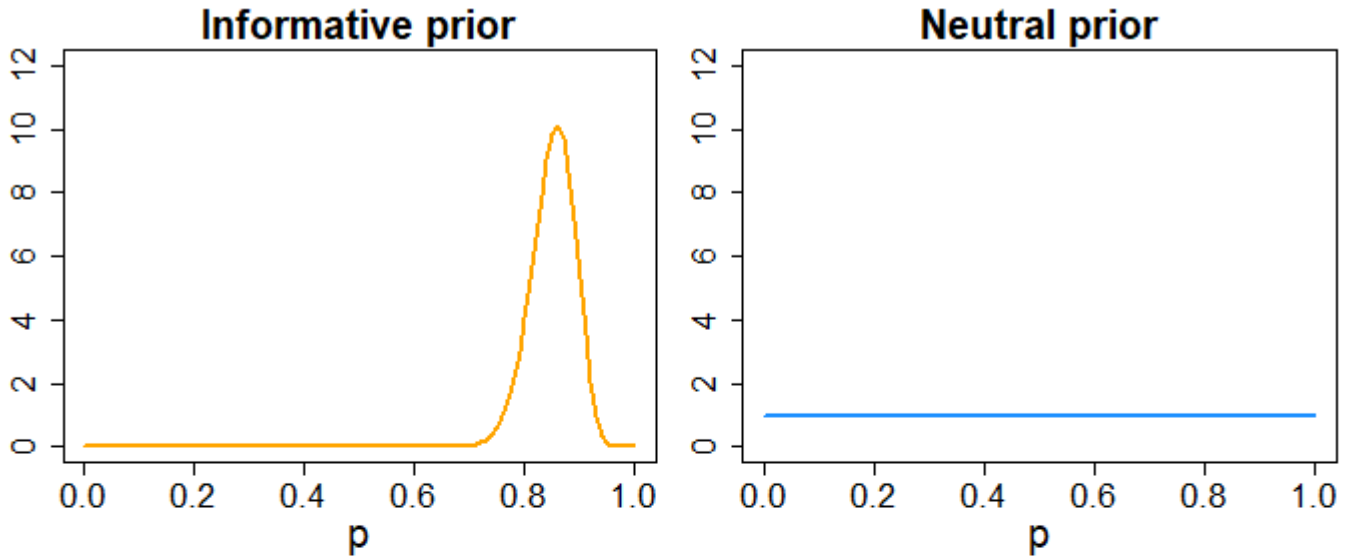
Robustification: get prepared for the unexpected

Solution[1]**:** *mix* informative prior (from past data) with a neutral one

$$\pi_R(p) \;\xrightarrow{w_r}\; \pi_1(p) \qquad \pi_R(p) \;\xrightarrow{1-w_r}\; \pi_0(p)$$



$\boldsymbol{w_r} \in [\mathbf{0}, \mathbf{1}]$ reflects how much we rely on past data

The smaller $\boldsymbol{w_r}$, the less rely on the past
…but the potential of Bayesian approach is reduced **(!)**

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1. Schmidli et al. (2014)

Self-Adapting Mixture (SAM) priors

SAM prior[2] dynamically adapts the level of borrowing from historical prior based on the *degree of consistence* between historical ($\mathrm{D_h}$) and new data (D).

$$p \sim \tilde{w} \cdot \pi_1(\theta) + (1 - \tilde{w}) \cdot \pi_0(\theta)$$

informative prior based on $\mathrm{D_h}$ and with mean θ_h

Uniform[0,1]

If $H_0: \theta = \theta_h$ (D and $\mathrm{D_h}$ **consistent**) and $H_1: \theta = \theta_h \pm 0.05$ (D and $\mathrm{D_h}$ in **conflict**), then

$$\tilde{w} \propto \frac{L_\theta(\mathrm{D}|H_0)}{L_\theta(\mathrm{D}|H_1)} = \frac{L_\theta(\mathrm{D}|\theta = \theta_h)}{\max\{L_\theta(\mathrm{D}|\theta = \theta_h \pm 0.05)\}}$$

The larger the conflict between D and $\mathrm{D_h}$, the less the borrowing from $\mathrm{D_h}$

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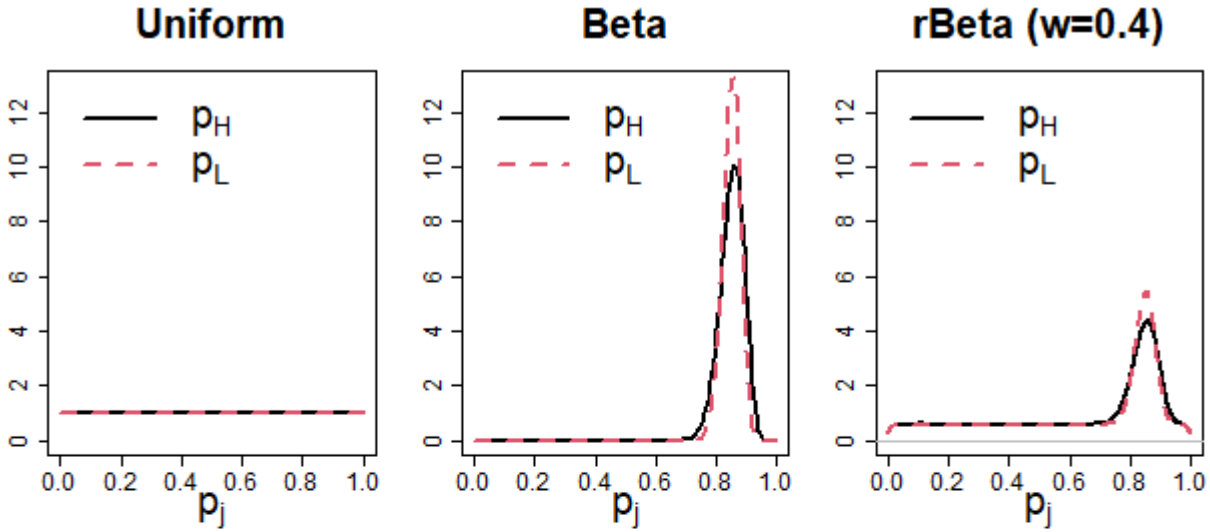
2. Yang et al. (2023)

Prior specifications (example)

- **Uniform:** $p_H, p_L \sim Unif\,[0,1]$
- **Beta:** $p_H \sim Beta\left(mean = \hat{p}_j^H\,, sd = 0.04\right)$

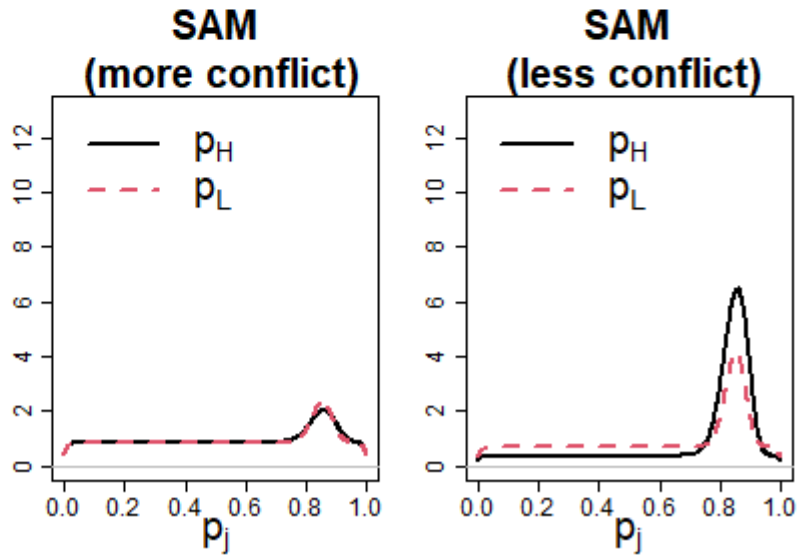
  $p_H \sim Beta\left(mean = \hat{p}_j^H\,, sd = 0.03\right)$

  with $\hat{\boldsymbol{p}}_{\boldsymbol{j}}^{\boldsymbol{H}} = \mathbf{0.85}$ **historical survival rate**



- **rBeta:** $p_j \sim w \cdot Beta_j + (1-w) \cdot Unif,\ w = 0.4,\ j = \{H, L\}$
- **SAM:** same as rBeta but with **dynamic** weight w_j determined by the level of prior-data conflict

  (N.B. the larger $|\hat{p}_j - \hat{p}_j^H|$, the larger the conflict)



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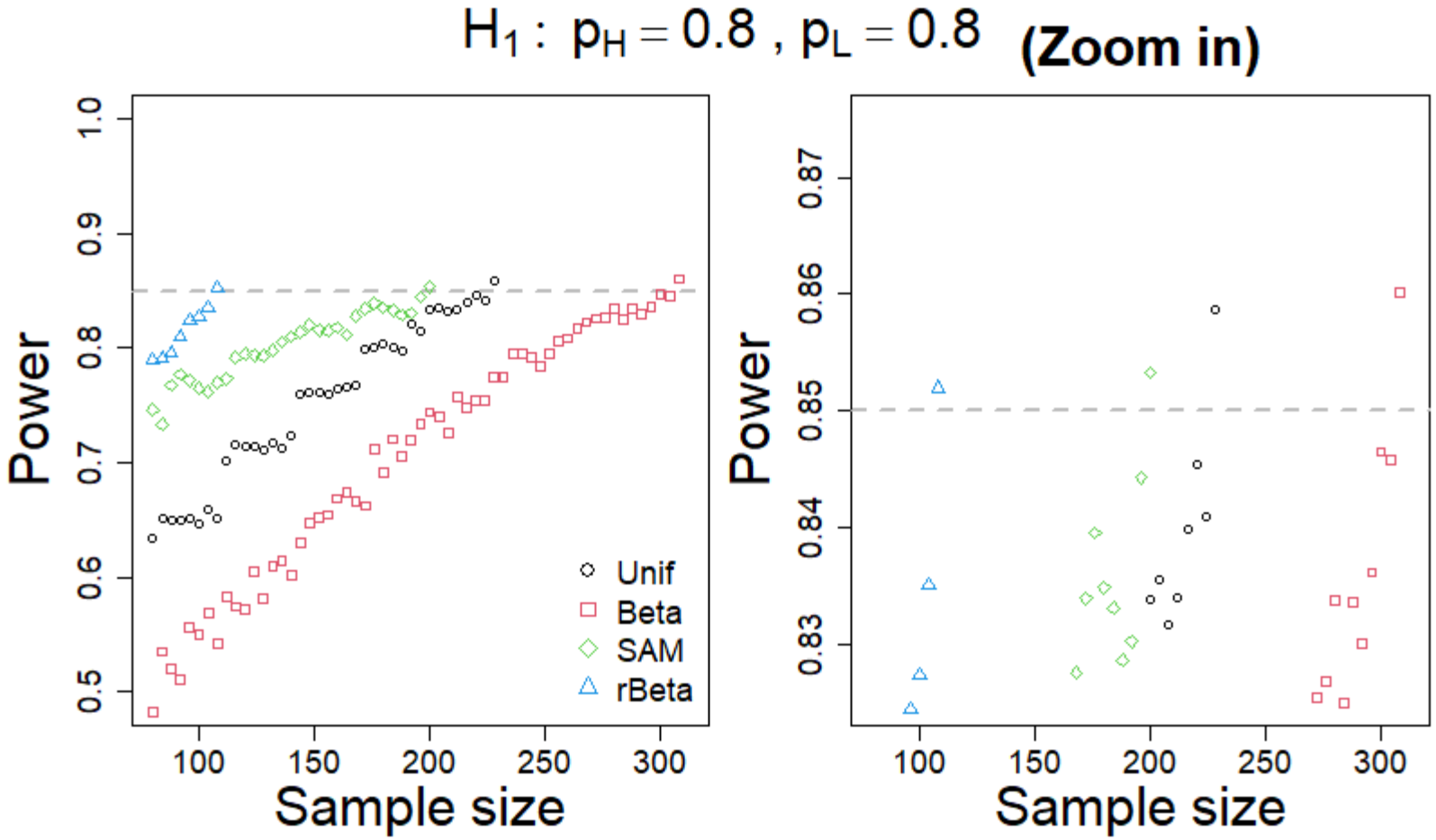
Sample size determination

- Forward search on grid of sample sizes $(n_C = n_L = n/2)$
- Stop when target power (85%) is achieved
- ξ calibrated to control $\alpha = 20\%$ under $H_0: p_H = 0.75, p_L = 0.65$



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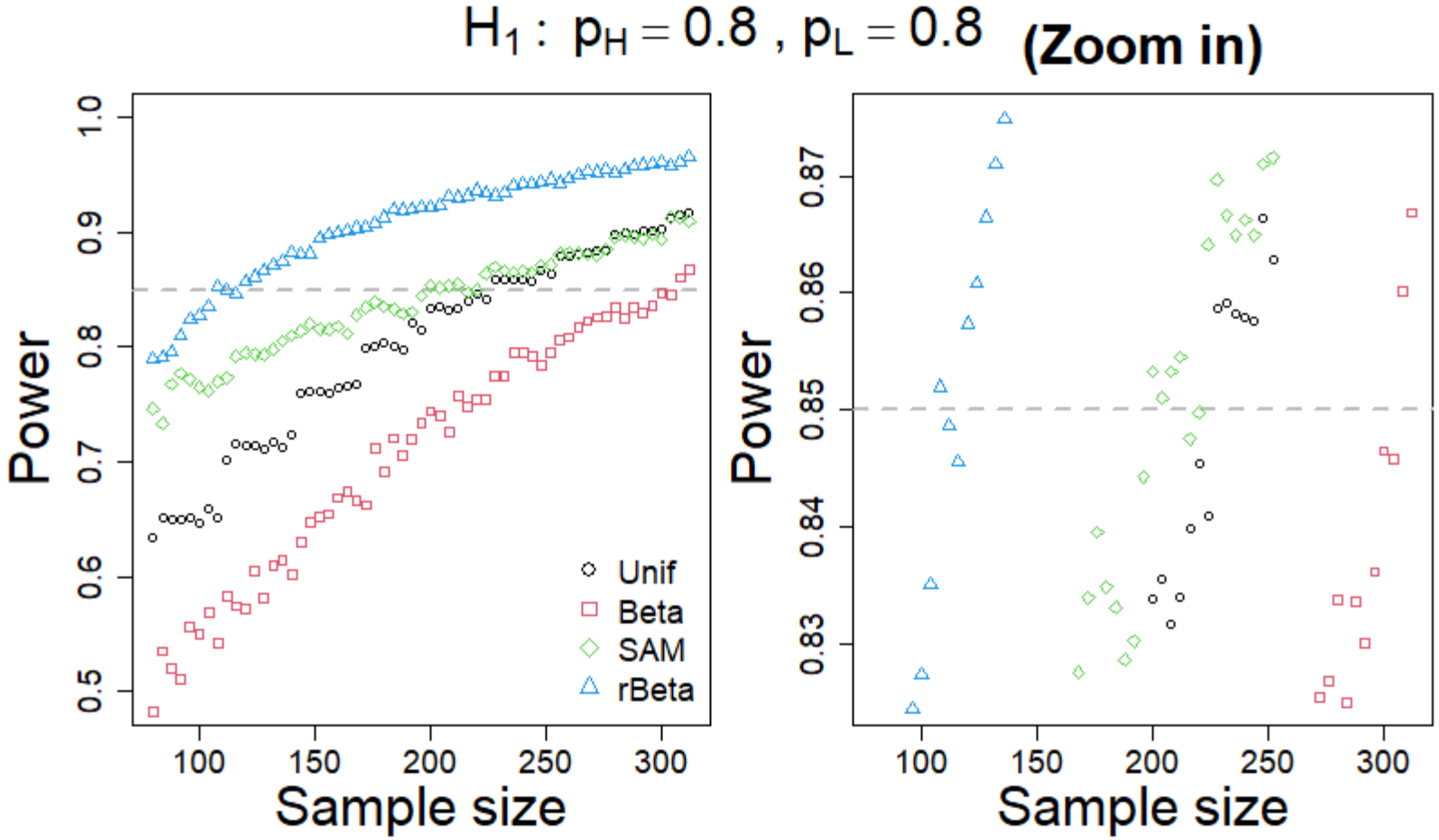
Results based on 50k posterior samples for each of the 200k replicas

Sample size determination

Caution:

Estimated power may decrease with sample size (simulation error?)

Counterintuive conclusion if we only rely on the power for a specific sample size



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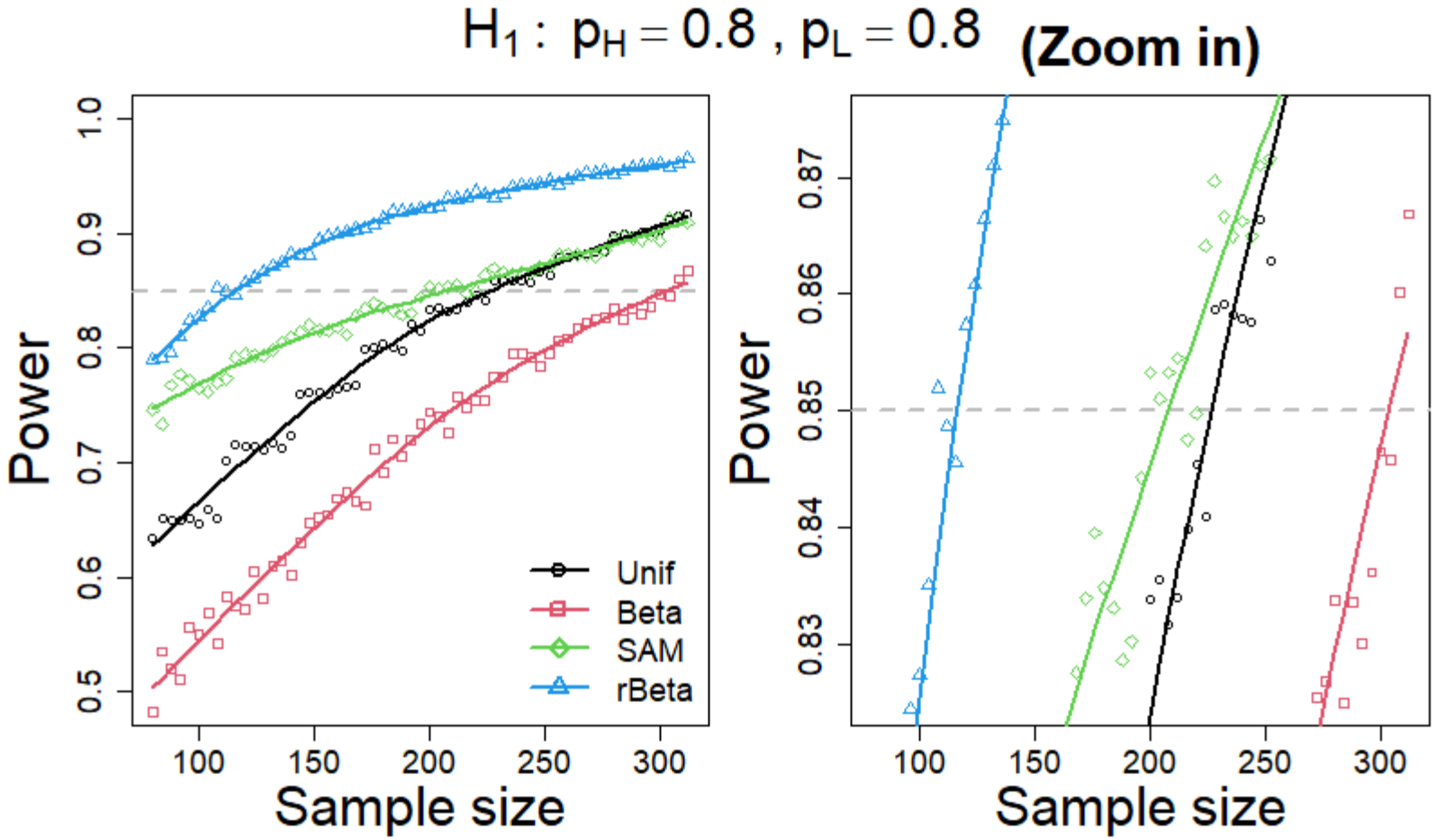
Results based on 50k posterior samples for each of the 200k replicas

Sample size determination

Solution:

Non-parametric regression to fit smooth power curve

More coherent interpretation of power vs sample size relationship



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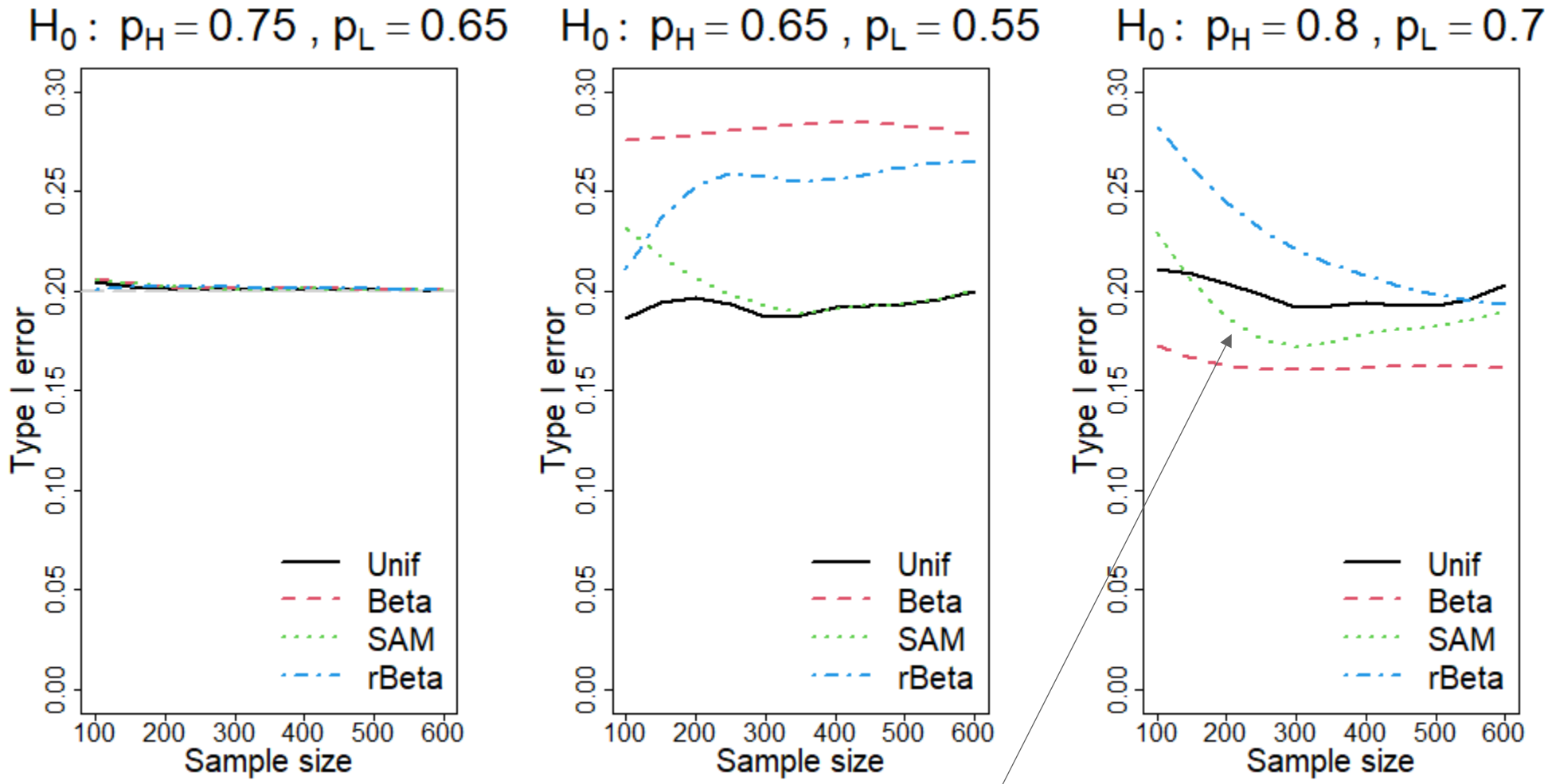
Results based on 50k posterior samples for each of the 200k replicas

What if the overall trend itself is non-monotonic?

Type-I error rates



Non-monotonic trend of type-I error

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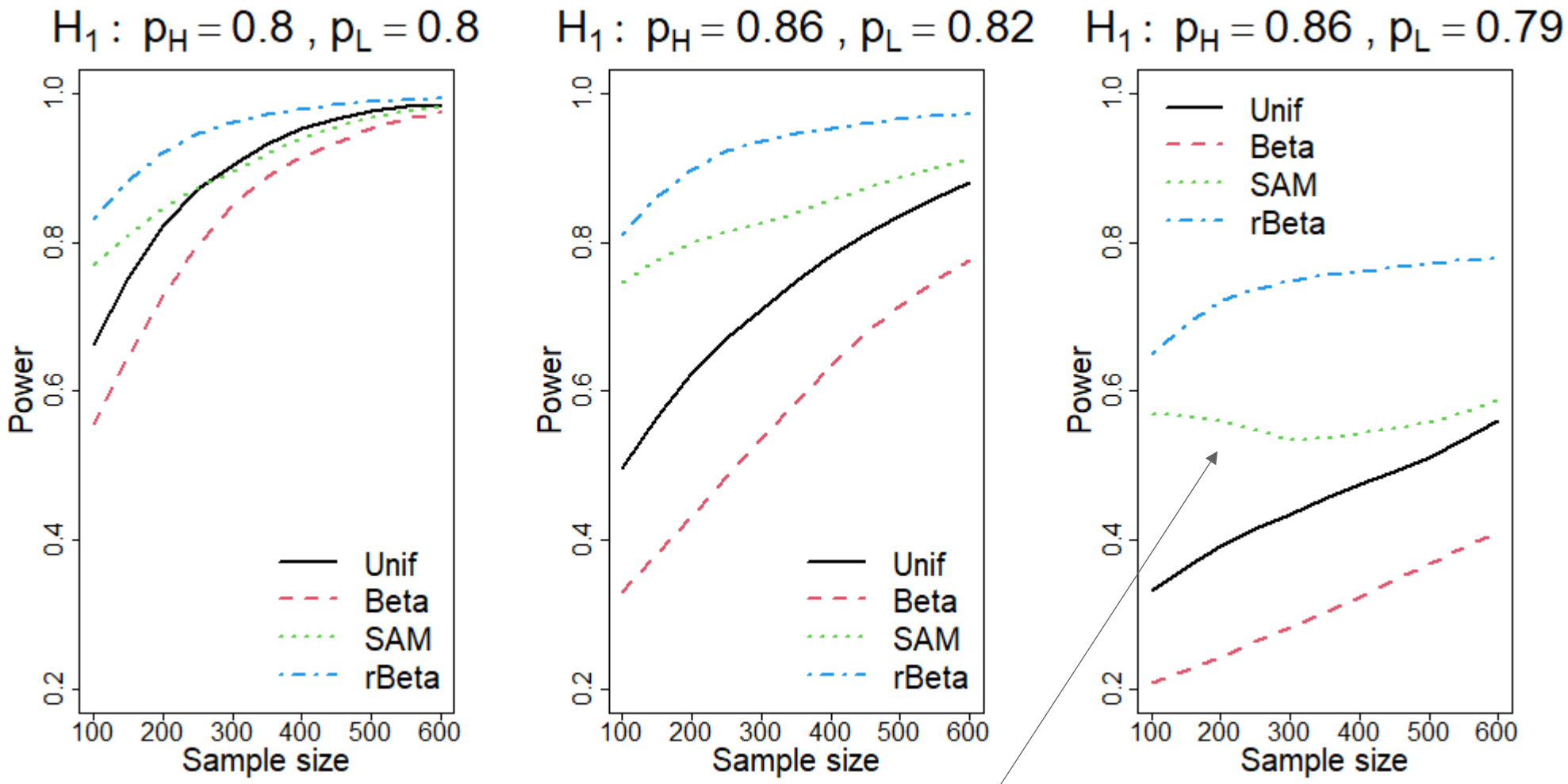
Power



Non-monotonic trend of power

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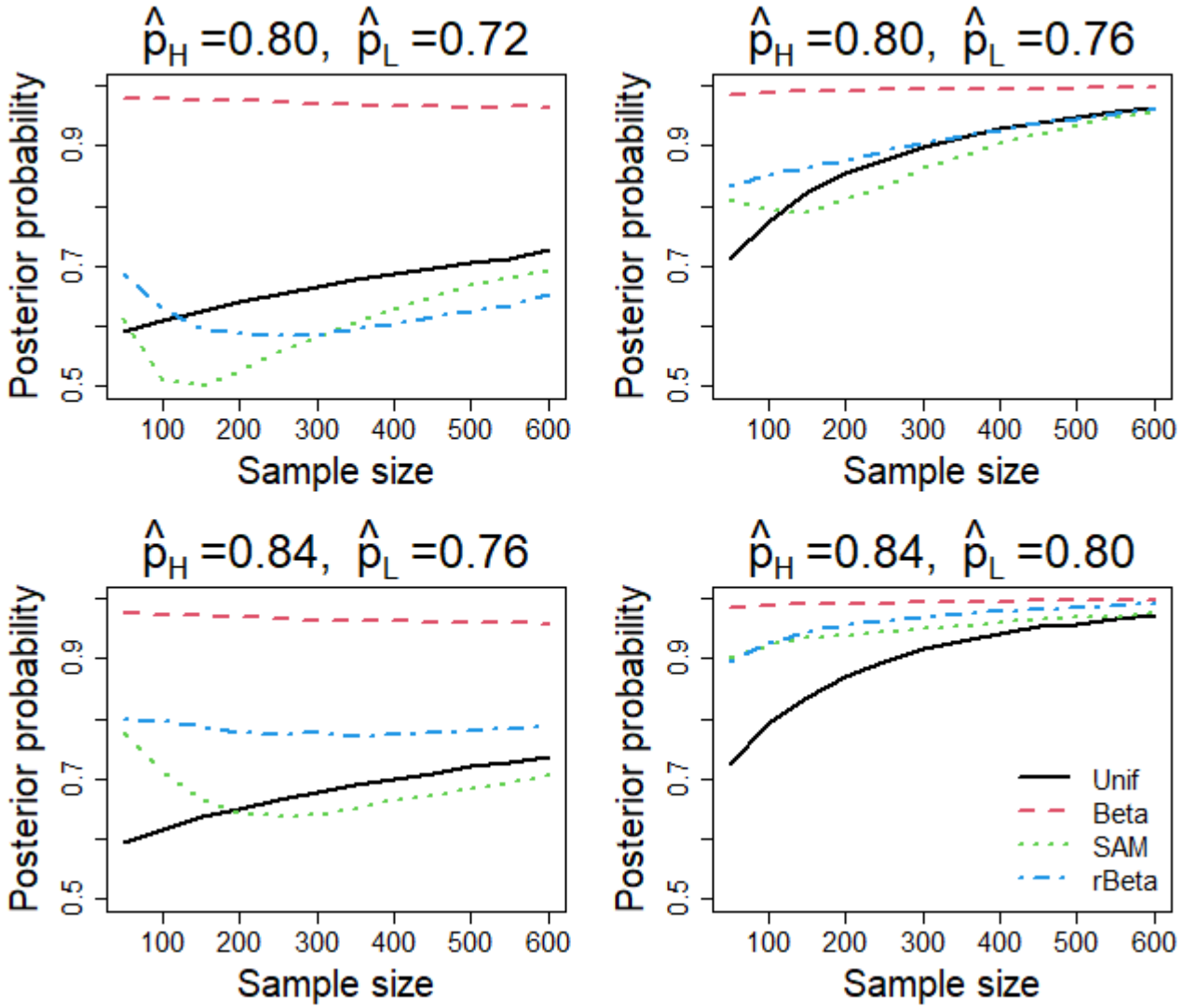
Closer look at posterior probability of H_0 being false

For fixed observed response rates $(\hat{p}_H, \hat{p}_L)$, posterior probability that H_0 is false based on SAM prior shows **evident non-monotonic behaviour** with sample size

Similar result obtained by Kopp-Schneider et al. (2020) on single-arm trial, with posterior probability decreasing with number of responses



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Final remarks

Dynamic borrowing of historical information allows for **prompt reaction to prior-data conflict**, by discounting the amount of information borrowed

…but careful use is needed:

- Bayesian **principle of independence** between prior and data is **violated**
- In some scenarios, the conflict between informative prior component and data may lead to **power curves that are non-monotonic with sample size**
- Sensitivity analysis for different sample sizes may be needed, above all **if more patients then expected are recruited**

Main references

Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D., & Neuenschwander, B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, *70*(4).

Yang, P., Zhao, Y., Nie, L., Vallejo, J. & Yuan, Y. (2023). SAM: Self-adapting mixture prior to dynamically borrow information from historical data in clinical trials. *Biometrics*, 79(4).

Kopp-Schneider A, Calderazzo S, Wiesenfarth M. (2020). Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control. *Biometrical Journal*, 62(2).

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Thank you for your attention!